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False asymmetry, pseudosymmetry, disorder, polymorphism and atomic displacement parameters

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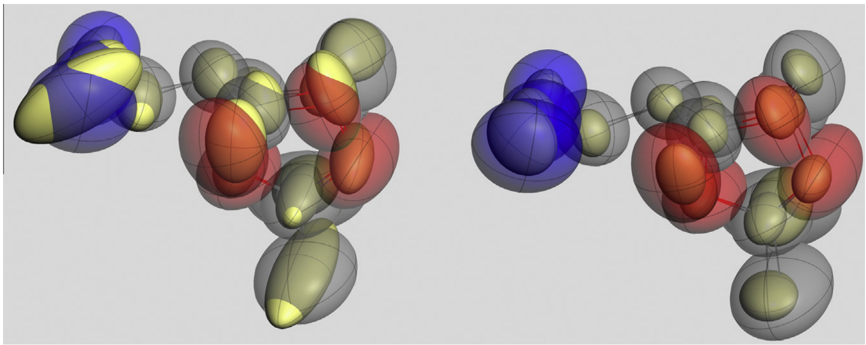
HIGHLIGHTS

- Two different kinds of very similar pseudosymmetric structures were studied.
- We quantified their attitude to change their symmetric arrangements to a higher symmetric state.
- The above mentioned findings were strengthened by means of an atomic displacement parameter analysis.
- We introduced a new parameter, δ, to quantify the adp anysotropicity.

GRAPHICAL ABSTRACT



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ABSTRACT

Two similar sugars, with chemical formulas differing only by the presence of a methyl group connected to the molecule backbones in different positions, crystallize in the monoclinic $P2_1$ space group giving rise to $Z' = 2$ structures. They both bear an azide side chain which is the principal responsible for the lack of a higher symmetry for one compound only. We analyzed their most relevant features by means of X-ray single crystal diffraction coupled with a quantitative estimation of their potential tendency to crystallize in a different space group with higher symmetry. The latter tendency of the most promising of the two compounds is commented in the light of the anisotropic behaviour of the atomic displacement parameters.

Introduction

According to Bernstein [1] who reviewed the evolution of the concept of polymorphism throughout more than one century, the most appropriate definition of a polymorph is the one given by McCrone in 1965 [2]: “A solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state”. To the more specific drug environment, in 1982, Byrn [3] addressed a similar definition of polymorphism as “the different crystal structures in which a compound can crystallize. Polymorphs are usually characterized by their space group and cell parameters.” The last FDA definition [4], regarding crystalline materials is “crystalline forms having different arrangements and/or conformations of the molecules in the crystal lattice.” Whatever the definition is, they all agree with a description of polymorphism at the molecular stage, which is based upon differences in crystal packing.

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The tendency of a system towards an ordered or disordered crystal packing has been addressed by several studies. There is a misleading misconception about disorder, only partially reinterpreted by means of basic scientific knowledge. In fact, we are naturally inclined to look for a symmetric – and consequently at least partially ordered – arrangement of objects in the space, as our brain needs a rational key to interpret the data corresponding to the reciprocal position of those objects in the space. It would be obviously harder recall all the numbers in a phone book without classifying them for example by name, and it would be surely more difficult finding books on a book shelf without previously having a knowledge about how they were classified on it. The same process is applied when trying to rationalize objects – in our case molecules – in a box – in our case a unit cell: knowing the rulebook and the mathematic operators, we can rebuild the exact position in a unit cell of each single molecule without forcing ourselves to commit each single coordinate of the molecule to memory. So, on the basis of the above mentioned reasoning, it seems obvious that every deviation from order and symmetry is interpreted as a flawed state. This is particularly true for pseudosymmetric structures i.e. in a broader meaning compounds showing a slight deviation from a complete symmetry. Pseudosymmetry has been always considered as a sort of metastable state, a characteristic that generally leads to a tendency of the system to give somehow different molecular arrangement, i.e. polymorphism. There are several types of pseudosymmetry with various different implications [5], but we are mainly interested in two of them: the first, that we will call from now on false asymmetry, although there is nothing false in it, describes an ill defined symmetry or a system where the addition or relocation of new pseudo elements of symmetry can give rise to the classification of a system in a higher group of symmetry, sometimes by means of the addition of a non-crystallographic element of symmetry. In the latter case, it results from the integration of an additional symmetry operator which does not give rise to a standard crystallographic setup – in other words it is a non-Fedorov pseudosymmetry [6]. The second kind is instead the result of a looser and broader volume of tolerance for the allowed vibration of each atom. It allows the balancing of the not perfectly symmetric layout of the building block of a unit cell by moving and shifting the atom positions within the range of the considered tolerance. A necessary although not sufficient condition is dealing with $Z' \geqslant 2$ structures i.e. structures with at least two independent fragments in the unit cell, being Z' the number of independent formula units in the unit cell.

For our investigation we chose two similar azides (Fig. 1), 2-C-Azidomethyl-2-deoxy-3,4-O-isopropylidene-d-ribono-1,5-lactone (**1**) [7] and 2-Azido-2-deoxy-3,4-O-isopropylidene-2-C-methyl-d-ribono-1,5-lactone (**2**) [8] whose pseudosymmetric $Z' = 2$ structures were solved and published some years ago by one of the authors of the present manuscript. As a consequence, at difference with what we generally deal with at the Cambridge Structural Database (CSD), we have their atomic displacement parameters (adps) available (actually they would have been available anyhow because they were published in a journal for which is mandatory depositing the crystallographic information file – .cif – corresponding to the studied structures). These data allowed us to perform a detailed study of the needed shift of each atom to fulfil, from the original pseudosymmetric arrangement, the requested symmetry layout. The whole analysis was carried out using a robust and already checked approach [9–13] which already allowed us to draw conclusions about the absolute stability of several different systems.

The two studied azides offer a different structural landscape: **1** is pseudosymmetric mainly for a non symmetric displacement of the nitrogen atoms of the flexible azide chain being the two fragments in the asymmetric unit arranged in a very symmetrical layout; **2**, on the other hand, shows the two molecules of the asymmetric unit tilted upside down from each other, thus loosing their opportunity to be easily symmetrised by "simple" operations. On the basis of our definition, we can include **1** in what we called the pseudosymmetry case, and **2** in the false asymmetry one. As a consequence, for the latter, either a bigger tolerance or new symmetry operators should be used to find a suitable super symmetric group to which it can belong.

In the present work we focused our attention on compound **1** coupling the analysis of its pseudosymmetry, performed by means of dedicated software, with the study of its adps. Their characteristics, more specifically, their magnitude together with their relative space distribution and directionality, as well as their anisotropies, have been analysed to predict and confirm the willingness and tendency of the studied compound to change its crystal structure. In other words, we studied its disorder to understand its tendency to be polymorphic.

Experimental methods

X-ray crystallography

2-C-Azidomethyl-2-deoxy-3,4-O-isopropylidene-d-ribono-1,5-lactone (**1**) and 2-Azido-2-deoxy-3,4-O-isopropylidene-2-C-methyl-d-ribono-1,5-lactone (**2**) were crystallized and their structures were collected, solved and refined as described in literature [8,9]. Their .cif were deposited in the CSD and can be found with the codes XAZSUN and FEDVOA, respectively.

In silico studies

The Materials Studio package (Accelrys Software Inc., San Diego) was used to perform the molecular mechanics (MM) and molecular dynamics (MD) calculations through the Discover module using the implemented AMBER force field (FF) [14]. The charges for each atom were obtained by means of the charge equilibration method [15]. The non-bond (NB) settings were different for the coulomb and the VdW interactions. For the VdW ones an atom based summation method (cut-off = 15.50, spline width = 5.00 and buffer width = 2.00 Å) with a long range energy correction (Tail Correction = 15.50 Å) was used. For what concerns the electrostatic interactions, the dielectric value ε was set to 1.0, and the Ewald summation method (accuracy = 0.0001 kcal/mol and update width = 5.00 Å) was used.

Protocols

The MD simulations started from the energy-minimized structures. The periodic boundary conditions (PBC) with NPT ensemble ($P = 0.0$, GPa and $T = 100$, 150, 200, 250, 275, 300, 325 and 350 K) were used for all the runs. In order to allow the cell to change both shape and volume, we used the Parrinello pressure control method [16], whereas Berendsen's thermostat with the default decay constant (0.01 ps) was used to control the temperature [17]. Transients of 1.5 ns were collected, after a 500 ps equilibration period, with 0.001 ps integration time and a sampling interval of 200 time-steps. The energy-optimized structures were obtained with the smart minimizer of the Discover module, satisfying a gradient of less than 0.1 kcal mol^{-1}.

Modeling

The structural models submitted to the simulations were generated on the basis of the single crystal X-ray structure (unit cells and atomic fractional coordinates). The periodic structural models were built by considering in the single unit cell the fractional parameters of each atom available in the .cif files.

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